frontiers | Frontiers in Science

TYPE Frontiers in Science Viewpoint
PUBLISHED 25 April 2024
DOI 10.3389/fsci.2024.1397048

OPEN ACCESS

EDITED AND REVIEWED BY
John T. Fallon,
East Carolina University, United States

*CORRESPONDENCE
David M. Engelthaler
dengelthaler@tgen.org

RECEIVED 06 March 2024
ACCEPTED 08 April 2024
PUBLISHED 25 April 2024

CITATION
Engelthaler DM. Genomic surveillance and pathogen intelligence.
Front Sci (2024) 2:1397048.
doi: 10.3389/fsci.2024.1397048

Genomic surveillance and pathogen intelligence

David M. Engelthaler*

Pathogen and Microbiome Division, Translational Genomics Research Institute, Flagstaff, AZ, United States

KEYWORDS

pathogen intelligence, whole genome sequencing, genomic epidemiology, drug resistance, microbial, One Health, SARS-CoV-2, pandemic preparedness

A Viewpoint on the Frontiers in Science Lead Article

Real-time genomic surveillance for enhanced control of infectious diseases and antimicrobial resistance

Key points

- Genomic surveillance provides both *epidemiological* pathogen intelligence and *clinical* intelligence (e.g., antimicrobial resistance markers) directly from clinical samples, which could enable early outbreak detection and precision responses.
- Large-scale collaborative sequencing and analysis of SARS-CoV-2 provided *epidemic* intelligence critical to tackling COVID-19, but gaps in linkages between surveillance systems, disunity of strategies, and variable global coverage need to be improved before the next pandemic.
- *Biologic* intelligence, through a One Health genomic surveillance perspective, could help identify and perhaps even stop the evolution of would-be pathogens before they emerge, as well as inform future countermeasures to emergent pathogens.

Introduction

In their lead article, Struelens et al. (1) provide us with a call-to-arms, or at least a call-to-sequencers, in the continued global fight against infectious diseases. They correctly identify that, while genomic-based pathogen detection and exploration has been advancing for the past two decades, it was the recent COVID-19 pandemic that highlighted both the global need and capability to bring sequencing and genomic analysis to the forefront in our continued war against pathogens. They lay out a strong case for this clinical and public health sea change and outline a roadmap to overcome the still significant hurdles related to: i) adoption of sequencing-based analysis into existing microbiology and surveillance programs and ii) data standardization and sharing between clinical and One Health-based partners. This viewpoint attempts to distill the argument for pathogen genomics adoption through the lens of *pathogen intelligence* gathering.

Pathogen intelligence?

Rather than being an assessment of a microbe's intellectual capacity, *intelligence* here refers to the gathering of microbial *intel* through genomic sequence analysis and the transformation of this information into actionable knowledge. A pathogen's genome stores these facts. It contains the genetic keys to the presence/absence of important genes, mutations, and other identity markers. It also stores information that, when combined with other sources of intel, can provide evidence on the microbe's origins, movements, and potential impacts. Through this lens we can describe four critical intelligence categories: i) epidemiological, ii) clinical, iii) epidemic, and iv) biological.

Epidemiological intel

Critically, pathogen intelligence allows for genomic epidemiology. Various phylogenetic analyses can provide statistical evidence of the relatedness of isolates, which in turn allows for accurate cluster or outbreak detection. Even more impactful, genomic surveillance can identify outbreaks sooner, even from the first cases (2)—well before a cluster is identified by "astute clinicians" or from the tabulation of case report data, which are still the gold standards in healthcare and public health, respectively. Additionally, such intel will allow for proper inclusion and exclusion assignment of suspect cluster cases. Both aspects are critical to the detection and ascertainment of the scope of outbreaks, while the latter is also an imperative for empirically proving that suspect clusters may be truly unrelated infections (3). Therefore, the use of genomic-based surveillance for early outbreak detection and more accurate outbreak case inclusion promises to significantly reduce healthcare costs, reduce morbidity and mortality, and improve public health efficiency by focusing investigations on only true genomically linked cases. Pathogen intelligence gathering allows for "precision epidemiology" to finally take its place alongside precision medicine.

Clinical intel

In addition to helping infection prevention and control departments detect outbreaks, a pathogen intelligence approach could provide actionable knowledge on the clinical features of the microbe, including antimicrobial resistance markers and potential virulence genes, as Struelens et al. highlight (1). While detection of resistance mutations and/or genes does not always capture a complete susceptibility profile for a given pathogen, current reference sequence databases do contain the vast majority of known resistance mechanisms (4). Of course, the mere presence of such targets does not equate to active resistance (e.g., some targets are constitutive housekeeping or efflux genes, and their presence alone reveals little about their resistance phenotype). The inclusion of transcript (i.e., mRNA) analyses can identify if such target genes are being modulated for resistance effect. Amplicon or targeted sequencing-based approaches allow for this intel to be gathered directly from clinical samples without the need for culture-based phenotyping or whole genome sequencing of isolates. The sequencing resolution provided by advanced techniques even allows for early pre-phenotypic resistance to be detected in time to potentially prevent actual onset resistance (5). Improved techniques for genome capture, target enrichment, host subtraction, and sequencing are helping to make clinical whole genome and even metagenome sequencing straight from clinical samples a reality (6) and could provide even more clinical intel on infections in the future.

Epidemic intel

As was made abundantly clear during the pandemic, the collective world of healthcare and public health needs better intel on microbial threats as they emerge and develop. Pathogen intel was notably used 15 years ago during the millennium's first true pandemic, the 2009 H1N1pdm09 "swine flu" pandemic. A handful of laboratories provided the critical sequencing data to track the origin and movement of the novel influenza strain as it moved out of Mexico and spread globally (7). Ten years later, thousands of labs around the world joined forces to conduct the largest sequencing effort in human history, tracking the macro- and micro-evolution of the SARS-CoV-2 virus. This moonshot effort provided a near real-time intelligence system for state and national policymakers and health officials to adjust response strategies to the changing variants and their critical phenotype-altering mutations. The world watched as mutations in the shape-shifting spike protein resulted in the virus' immune escape, therapy resistance, and cell invasion strategies and capabilities, ultimately resulting in the pandemic-ending Omicron variant and its endless subvariants. However, despite the enormity and intensity of the sequencing and analysis efforts, the gaps in linkages between surveillance systems, disunity of local, national, and global strategies, and variable coverage across global populations need to be improved before the next pandemic (1).

Biological intel

A pathogen intelligence approach could also provide expansive information on the biology, ecology, and evolutionary history of the microbe as a biological, rather than etiological, agent. Beyond focusing on the immediate intel for patient or population health, we can gather intel on the pathogen as a microbe, and how it lives and thrives in its environment. This is critical, as the clinical/epidemiological anthropomorphic view is a highly distorted perspective, ignoring that most pathogens are just microbes with some pathogenic potential and often the intel needed to respond to or mitigate a health threat is in the biology or ecology of the microbe. For example, it is now thought that *Cryptococcus neoformans* is an accidental animal fungal pathogen that has formed intracellular defenses through its natural survival strategies to endure amoeba engulfment in its natural habitat (8).

Genomic analysis can identify which genetic features drive this natural survival mechanism, which may in turn contribute to future medical countermeasure strategies. With genomics, we can place a pathogenic microbe in the phylogenetic context of its relevant taxonomical relationships to understand what has been lost or gained genetically to create pathogenic descendants from a non-pathogenic family history. For example, genomics could demonstrate that another pathogenic fungal genus, *Coccidioides*, the etiologic agent of Valley fever, has both lost the plant protease genes of its relatives and gained animal protease genes, radically transforming it into a mammalian pathogen (9). Phylogenetics also holds the key to understanding where, when, and how newly identified pathogens emerge. Sticking with *Coccidioides*, this fungus, predominantly found in the arid thermic soils of the American southwest, was recently found both in soils and patients in faraway south-central Washington (WA). Genomic analyses have shown that this is a clonal population in WA, and is likely hundreds to thousands of years old, helping mycologists and public health scientists to understand its relative importance in the natural history of the fungus and the epidemiology of the disease today (10). Given the close tie to animals and the environment for many microbes that become pathogens, a One Health approach to biological intel gathering is a necessity. Metagenomics and genomic clock analyses provide intel to help understand the One Health origins of everything: from HIV and *Mycobacterium tuberculosis* to *Candida auris*. Such biological intel on microbial family secrets may hold the key to not only better treatment of current infections but perhaps also identification and prevention of would-be pathogens before they emerge.

Statements

Author contributions

DE: Conceptualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The author declares that the research was conducted in the absence of financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Struelens MJ, Ludden C, Werner G, Sintchenko V, Jokelainen P, Ip M. Real-time genomic surveillance for enhanced control of infectious diseases and antimicrobial resistance. *Front Sci* (2024) 2:1298248. doi: 10.3389/fsci.2024.1298248

2. Yaglom HD, Bhattarai R, Lemmer D, Rust L, Ridenour C, Chorbi K, et al. Large clusters of invasive *emm*49 Group A *Streptococcus* identified within Arizona healthcare facilities through statewide genomic surveillance system, 2019–2021. *J Infect Dis* (2024), jiae086. doi: 10.1093/infdis/jiae086

3. Roe CC, Horn KS, Driebe EM, Bowers J, Terriquez JA, Keim P, et al. Whole genome SNP typing to investigate methicillin-resistant *Staphylococcus aureus* carriage in a health-care provider as the source of multiple surgical site infections. *Hereditas* (2016) 153:11. doi: 10.1186/s41065-016-0017-x

4. Alcock BP, Huynh W, Chalil R, Smith KW, Raphenya AR, Wlodarski MA, et al. CARD 2023: expanded curation, support for machine learning, and resistome prediction at the Comprehensive Antibiotic Resistance Database. *Nucleic Acids Res* (2023) 51(D1):D690–9. doi: 10.1093/nar/gkac920

5. Engelthaler DM, Streicher EM, Kelley EJ, Allender CJ, Wiggins K, Jimenez D, et al. Minority *Mycobacterium tuberculosis* genotypic populations as an indicator of subsequent phenotypic resistance. *Am J Respir Cell Mol Biol* (2019) 61(6):789–91. doi: 10.1165/rcmb.2019-0178LE

6. Terrazos Miani MA, Borcard L, Gempeler S, Baumann C, Bittel P, Leib SL, et al. NASCarD (Nanopore Adaptive Sampling with Carrier DNA): A rapid, PCR-free method for SARS-CoV-2 whole-genome sequencing in clinical samples. *Pathogens* (2024) 13(1):61. doi: 10.3390/pathogens13010061

7. Smith GJD, Vijaykrishna D, Bahl J, Lycett SJ, Worobey M, Pybus OG, et al. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. *Nature* (2009) 459(7250):1122–5. doi: 10.1038/nature08182

8. Fu MS, Liporagi-Lopes LC, Dos Santos SR Jr, Tenor JL, Perfect JR, Cuomo CA, et al. Amoeba predation of *Cryptococcus neoformans* results in pleiotropic changes to traits associated with virulence. *mBio* (2021) 12(2):e00567–21. doi: 10.1128/mBio.00567-21

9. Sharpton TJ, Stajich JE, Rounsley SD, Gardner MJ, Wortman JR, Jordar VS, et al. Comparative genomic analyses of the human fungal pathogens *Coccidioides* and their relatives. *Genome Res* (2009) 19(10):1722–31. doi: 10.1101/gr.087551.108

10. Engelthaler DM, Chatters JC, Casadevall A. Was *Coccidioides* a pre-Columbian hitchhiker to Southcentral Washington? *mBio* (2023) 14(2):e00232–23. doi: 10.1128/mbio.00232-23